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Effect of octreotide on blood glucose and counterregulatory hormones in insulin-dependent diabetic patients: the role of dose and route of administration

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Abstract *Objective*: The role of the dose and route of administration of octreotide in addition to insulin on daily blood glucose, growth hormone, glucagon, cortisol and adrenaline profiles in 7 insulin-dependent diabetic patients have been studied. Octreotide was administered either as multiple subcutaneous injections (50 μg three times daily, total dose 150 μg) or by continuous subcutaneous infusion of lower 62.5 μg 24/h and 112.5 μg 24/h.
Results: Blood glucose and growth hormone concentrations were lowered by octreotide in a similar manner regardless of the route of administration and dose. Glucagon concentrations at 12 and 16 h were reduced by all octreotide doses, but fasting at 20, 24 and 04 h concentrations were lowered only by 113 μg given by continuous infusion. Cortisol and adrenaline concentrations were not modified.
Conclusions: Thus, low doses of octreotide administered by continuous infusion in addition to standard insulin treatment displayed the same hypoglycaemic effect as larger doses given by multiple injections without causing adverse-effects or hypoglycaemic episodes.

Key words Glycaemia, Diabetes (IDDM), Octreotide; glucagon, growth hormone

Introduction

The capacity of somatostatin to reduce postprandial hyperglycaemia in insulin-dependent diabetic patients [1, 2] has focused much attention on the possible use of this hormone to control their hyperglycaemia. Unfortunately, the clinical use of somatostatin is hampered both by it's short half-life and by the fact that it can only be administered by the intravenous route. To overcome these problems, a somatostatin analogoue was produced (octreotide) that has a longer half-life than somatostatin, and which can be administered subcutaneously [3]. Compared to somatostatin, octreotide possesses a more selective inhibitory action on hyperglycaemia hormones, such as growth hormone and glucagon [3]. Some studies show that subcutaneous administration of octreotide reduces glycaemia in insulin-dependent diabetic patients [4–9]. However, to the best of our knowledge it is still not settled whether there is any difference in its effect on the daily profiles of blood glucose and counterregulatory hormones when octreotide is administered by different routes and in different doses.

The aim of the present study was to evaluate whether multiple subcutaneous injections or continuous subcutaneous infusion of different doses had different effects on daily blood glucose, growth hormone, glucagon, cortisol and adrenaline concentrations in insulin-dependent diabetic patients with poor metabolic control.

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Materials and methods

We studied 7 C-peptide negative insulin-dependent diabetic patients, (5 females and 2 males) aged 24 to 64 y (mean with (SD) = 46.3 (17.6) y. The mean duration of disease was 19.3 (9.47) y and their mean Body Mass Index was 25.2 (2.71) kg · m^{-2}. The patients were treated with insulin three-times a day (soluble before breakfast and lunch, and intermediate or a mixture of soluble and intermediate before dinner), and their mean insulin requirement was 48 (8.6) I.U./daily. They all exhibited poor metabolic control (glycosylated haemoglobin: 9.1 (1.2)%) during the week prior to the study. Five patients showed retinopathy and two also had autonomic neuropathy.

Daily blood glucose profiles were evaluated either during treatment with insulin alone or during combined insulin-octreotide administration.

Two different routes of administration of octreotide were randomly used with a two day wash-out interval:

a) multiple subcutaneous injections This comprised subcutaneous injection of octreotide 50 μg at 8, 15, and 23 h; total dose/24 h 150 μg).

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b) continuous subcutaneous infusion In this protocol octreotide was infused subcutaneously for 24 h (from 08.00 h until 8.00 h on the following day) using a micropump (Quark Miles Italy). Two doses (low and median – 50 and 100 μg) of octreotide were used, and both were preceeded by a rapid single bolus of 12.5 μg (the total doses infused in 24 h was 62.5 μg and 112.5 μg, respectively). During the study the patients did not change their insulin dose or diet.

Daily blood glucose profiles (in blood samples taken out every 4 h), growth hormone, glucagon, cortisol, and adrenaline concentrations (in blood samples taken out at 8, 12, 16 and 20 h) were evaluated. In four patients hormonel levels were also assayed at 24 and 04 h. Patients stood for at least 30 minutes before blood sampling.

Blood glucose was assayed by the gluco-oxidase method using an Autoanalyser, growth hormone, immunoreactive glucagon, and cortisol were measured by radioimmunoassay using reagents supplied by Biodata (Italy) and adrenaline by HPLC with electrochemical detection (Recipe Pharma, Munich, Germany).

Statistical analysis employed by one-way analysis of variance followed by Neuman Keul's procedure. Results are expressed as means with SEM.

Patients gave their informed consent to participation in the study which was conducted according to the Declaration of Helsinki and was approved by the local Ethics Committee.

Results

A marked reduction in blood glucose concentrations was observed during treatment with octreotide either given by multiple subcutaneous injections ($F = 23.1$, $P < 0.0001$) or by continuous subcutaneous infusion in two different doses (112.5 μg/24 h: $F = 34.2$, $P < 0.0001$; and 62.5 μg/24 h: $F = 5.74$, $P < 0.03$) compared insulin alone (Fig. 1). In contrast, there was no difference in glycaemia during octreotide treatment by multiple subcutaneous injections and either of the two continuous subcutaneous infusions.

Octreotide treatment also significantly ($P < 0.0004$) lowered daily growth hormone concentrations both when administered by multiple subcutaneous injection or by continuous subcutaneous infusion at different dose rates as compared with insulin alone (Fig. 2). A significant reduction was observed at 4 and 04 h in the four patients in whom growth hormone was assayed during the night (Fig. 3). Glucagon concentrations at 12 and 16 h were lowered by octreotide independent of the method of administration. In contrast, we observed no significant reduction in the fasting or 20 h concentrations of glucagon after administration of octreotide both by multiple subcutaneous injections or by continuous subcutaneous infusion ($62.5\ \mu g \cdot 24\ h^{-1}$) as compared to treatment with insulin alone. A significant reduction ($P < 0.02$) occurred only when octreotide was administered SC at 113 μg/24 h (Fig. 4). In the four patients in whom nocturnal glucagon concentrations were assayed, there was a significant reduction only when 113.5 μg octreotide was given by continuous SC infusion (Fig. 5). Cortisol concentrations showed a circadian rhythm 412 (75) $nmol \cdot l^{-1}$ at 08 h, 350 (79) $nmol \cdot l^{-1}$ at 12 h, 235 (61) $nmol \cdot l^{-1}$ at 16 h, 194 (69) $nmol \cdot l^{-1}$ at 20 h), and this was not modified by octreotide.

Adrenaline profiles (205 (44) $pmol \cdot l^{-1}$ at 08 h, 181 (32) $pmol \cdot l^{-1}$ at 12 h, 234 (41) $pmol \cdot l^{-1}$ at 16 h, 218 (36) $pmol \cdot l^{-1}$ at 20 h) were not changed by octreotide. The nocturnal profiles of cortisol and adrenaline, too, were not affected by octreotide.

The side effects of octreotide were modest and consisted of some diarrhoea; three patients suffered hypoglycaemic attacks in the afternoon after SC injection that disappeared spontaneously. Neither side effect occurred when the continuous subcutaneous infusion of octreotide was employed.

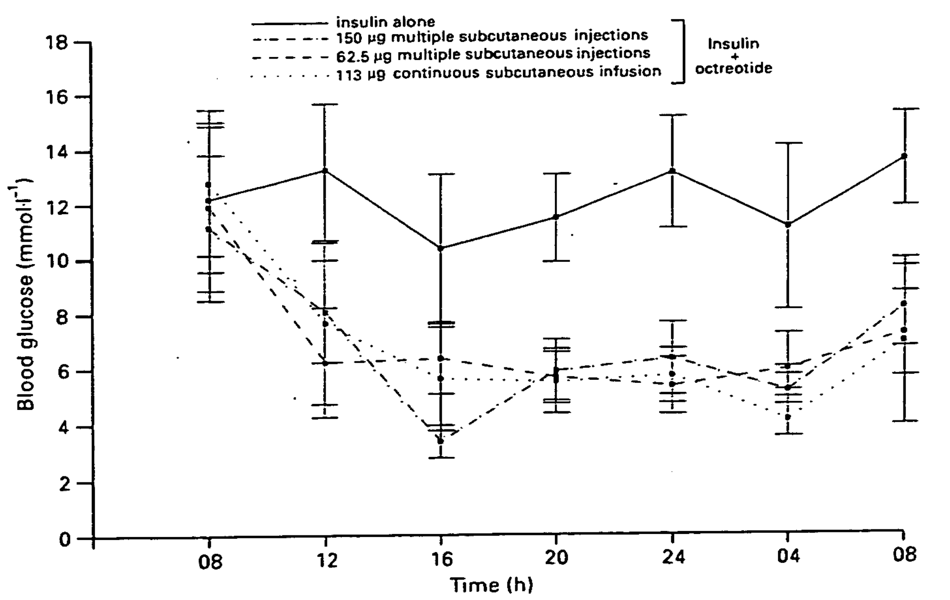

Fig. 1 Blood glucose (mean values with SEM) during insulin treatment alone and with octreotide given by multiple SC injection or continuous SC infusion in insulin dependent diabetic patients

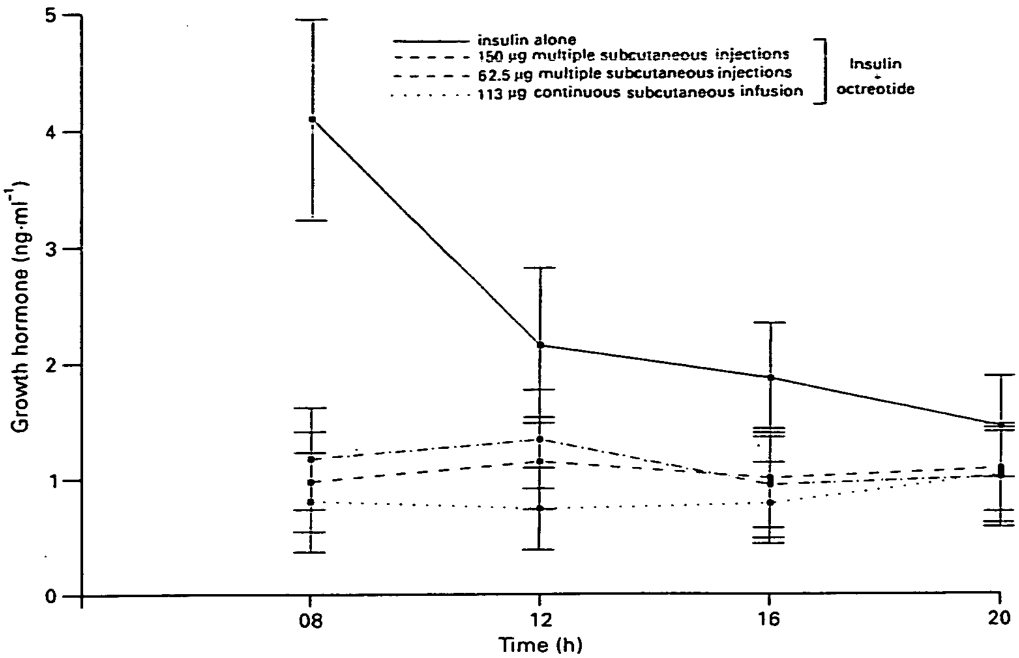

Fig. 2 Growth hormone concentrations (mean with SEM) during insulin treatment alone and with octreotide given by multiple SC injection or continuous SC infusion in insulin dependent diabetic patients

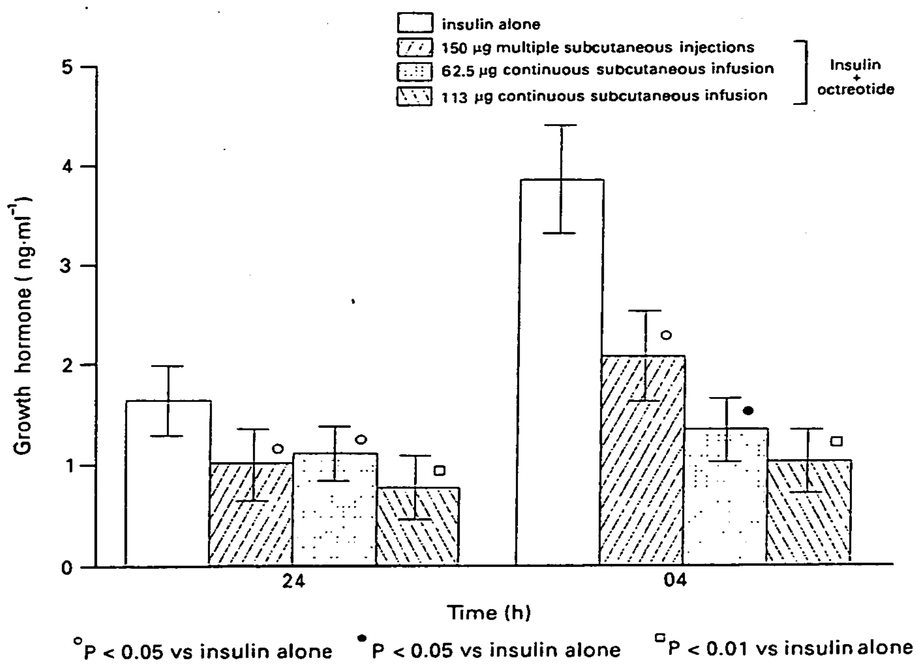

Fig. 3 Growth hormone levels at night (mean with SEM) during insulin treatment alone and with octreotide given by multiple SC injection or continuous SC infusion at different doses in four insulin dependent diabetic patients

Discussion and conclusion

We have demonstrated that octreotide may significantly reduce daily glycaemia in insulin-treated diabetic patients with poor metabolic control. It was effective when administered either by multiple SC injections or by continuous SC infusion of two different doses with a micropump. Our results agree with other studies conducted under different experimental conditions, in most of which octreotide was injected subcutaneous in the dose of 50 µg before each of three meals [4–7].

A reduction in the insulin requirement together with improved metabolic control has also been reported with the lower dose of octreotide (35 µg) administered every 8 hours for 8 consecutive weeks [8]. Timing and dosage

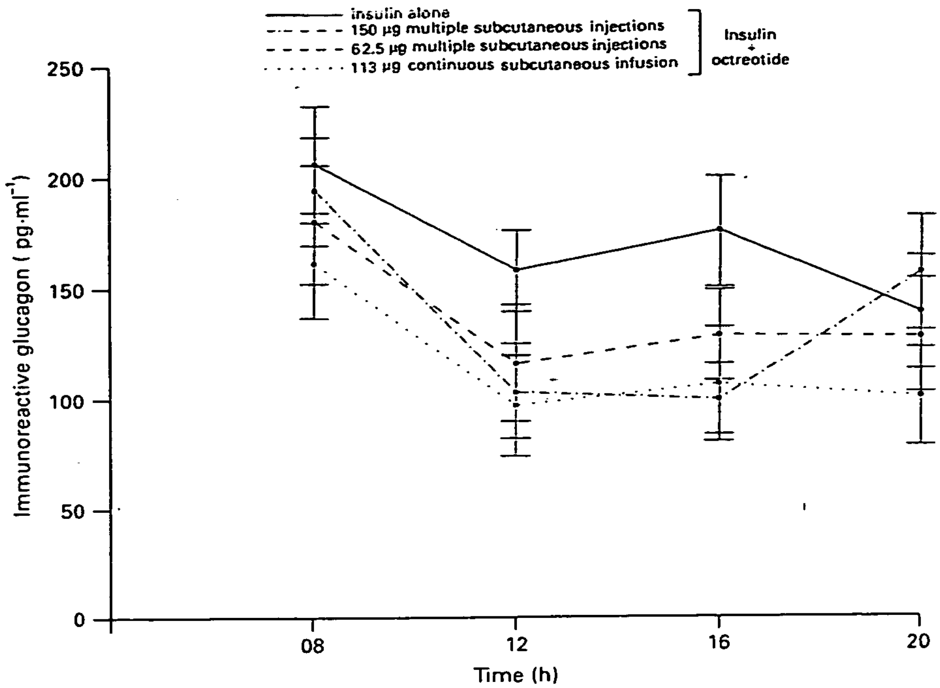

Fig. 4 Immunoreactive glucagon (mean with SEM) during insulin treatment alone and with octreotide given by multiple SC injection or continuous SC infusion in insulin dependent diabetic patients

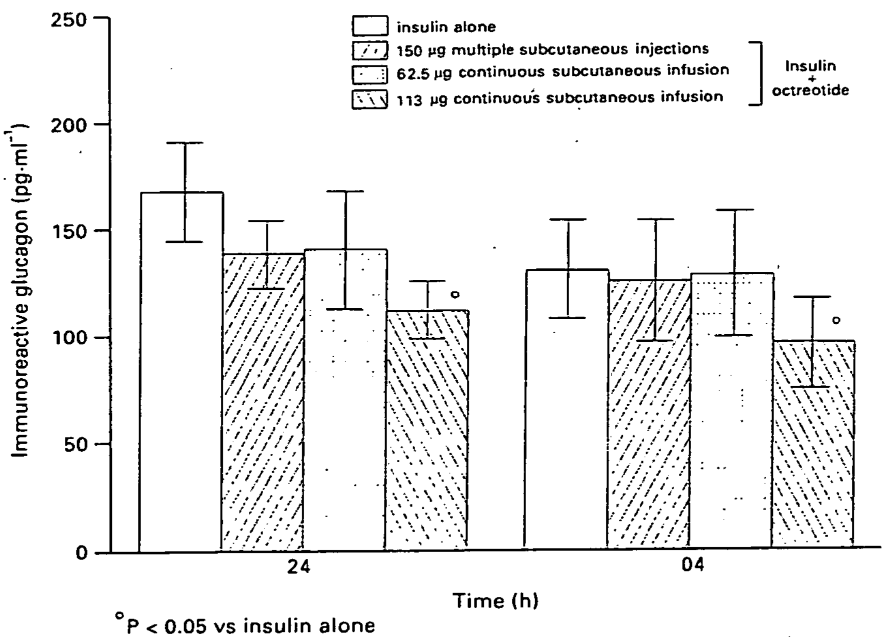

Fig. 5 Immunoreactive glucagon levels at night (mean with SEM) during insulin treatment alone and with octreotide given by multiple SC injection or continuous SC infusion in four insulin dependent diabetic patients

appear to be important for the metabolic action of octreotide to be displayed as lower doses (either 10 or 50 µg twice daily) neither permitted a reduction in the insulin requirements nor improved metabolic control in insulin-dependent diabetic patients [10]. Octreotide may exhibit its metabolic effect at several levels, including reduced intestinal glucose uptake [11–13], and inibition of growth hormone and glucagon secretion [3, 5, 7, 9, 14]. That octreotide may exhibit it favourable effects in diabetic patients through inhibition of the counterregulatory hyperglycaemic hormones is further emphasised by the observation that when octreotide fails to reduce growth hormone and glucagon concentrations it also fails to affect glycaemia [10]. It has been suggested that the inhibitory action of octreotide on glucagon may be greater than that on growth hormone

in relation to postprandial hyperglycaemia in diabetic patients [6].

In our study octreotide was effective in reducing daytime and nocturnal growth hormone profiles regardless of the method of administration of the low and median doses, but glucagon concentrations were reduced only at 12 and 16 h. In contrast, it was only during the continuous infusion of 113 µg/24 h that octreotide also reduced fasting, 20, 24 and 04 h glucagon concentrations. However this reduction in glucagon did not lead to much of in glucose concentrations.

Morning hyperglycaemia was also reduced by octreotide administration. The increase in glycaemia in the morning (dawn phenomenon) has been related to an increase in growth hormone [14] and the data reported following octreotide administration are few and controversial, with one study claiming beneficial effects [4], and others reporting negative results after an evening injection [15, 16]. These discrepancies may be due to different nocturnal levels of glycaemia and/or to an insufficient plasma concentration of octreotide because its level falls below the threshold for inhibition of growth hormone secretion within 4–6 h after an injection [16, 17]. In our study the continuous infusion and the multiple injections of octreotide lowered both nocturnal and morning growth hormone concentrations and this reduction, together with improved metabolic control during the night, could have contributed to the maintainance of the low level of glycaemia in the morning as well.

The behaviour of cortisol and adrenaline after octreotide in insulin-dependent diabetic patients has rarely been considered [15]. Our results showed that their concentrations were not affected by octreotide, so any role of these counterregulatory hormones in the improved metabolic control induced by octreotide can be excluded. These findings may be important since preserved adrenaline and cortisol responses may be the only defence against hypoglycaemia when glucagon and growth hormone secretion is impaired by octreotide.

The following conclusions may be drawn from our study:

1) octreotide lowered daily glycaemia levels in insulin-treated diabetic patients with poor metabolic control when administered either by multiple subcutaneous injections or as a continuous SC infusion;
2) low doses administered by continuous SC infusion displayed a similar hypoglycaemic effect to that of larger doses given by multiple SC injections;
3) growth hormone was suppressed by both methods of administration of octreotide, whereas the only middose given by continuous SC infusion reduced glucagon levels at all times;
4) cortisol and adrenaline were not modified by octreotide;
5) side-effects and hypoglycaemic episodes did not occur when octreotide was administered by continuous SC infusion as compared to multiple SC injections.

Continuous subcutaneous infusion at low doses may be the more suitable route for octreotide administration in order to improve poorly controlled insulin-dependent diabetic patients. Medium doses by continuous subcutaneous infusion were more effective in reducing glucagon concentrations. However long-term studies are needed to evaluate the clinical value of such treatment.

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